REMARKS

Rejections under §101 and §112, first paragraph

Ephrins are members of a recognized family of signaling molecules that are involved in a number of important physiological and developmental processes. In a search of the Medline database, 546 different articles were identified that contained the term "ephrin." See, Exhibit 1. Ephrins are also described in at least 23 issued patents and 160 published patent applications. See, Exhibit 2. Very clearly, ephrins comprise a "well-known" class of molecules that are widely used by the scientific community.

As indicated in the specification, the claimed ephrin subtype – EpA6 – is a tyrosine kinase receptor. Applicant explained its importance on Page 2 of the specification: "Eph receptor tyrosine kinases and their ligands, ephrins, play functional roles during development, especially in pattern formation and morphogenesis. They are involved in a variety of developmental processes, including, e.g., cell adhesion, retinocollicular mapping, synapse formation, and in the organization of the peripheral vestibular system. See, e.g., Matsunaga et al., *Eur. J. Neurosci.*, 12:1599-1616, 2000; Klein, *Current Opinion in Cell Biology*, 13:196-203, 2001."

Contrary to the statements made in the Office action, ephrin receptors have a characterized tyrosine kinase activity. For example, an activity of this receptor type is described on Page 2 of the specification: "EpH receptors behave similarly to other tyrosine kinase receptors, i.e., binding of the ephrin ligand causes receptor dimerization and trans-phosphorylation by the cytoplasmic kinase domains of two receptor molecules (Klein, *Current Opinion in Cell Biology*, 13:196-203, 2001)."

In addition to the enzyme activity, the present application discloses that EphA6 is highly restricted to the brain, pancreas, and testis. See, Specification, Fig. 1, and Page 2, lines 26-31. The other cell types in which it is expressed (i.e., brain and testis) do not detract from its utility

as a tissue marker, e.g., as a pancreas marker. For instance, in a patient with pancreatic cancer, it can be used to detect metastatic pancreatic cells, e.g., when metastasis from a primary pancreatic tumor site has occurred, or in a biopsy of the pancreas to identify the pancreatic tissue. See, e.g., Specification, Page 33, lines 1-10; Page 24, beginning on line 29.

Moreover, pancreatic and brain cells share a common signaling pathway, and thus can be used as a marker in the burgeoning field of stem cell engineering. As summarized in the specification on Page 3: "Components of the Notch signaling pathway are expressed during both neuronal and pancreatic cell differentiation (Apelqvist et al., *Nature*, 400:877-881, 1999; Jensen et al., *Nature Genet.*, 24:36-44, 2000). Furthermore, embryonic stem (ES) cells which display neuronal cell markers have been induced to differentiate into insulin-producing pancreatic islet cells, indicating a close relationship between the two cell types (Lumelsky et al., *Science*, 292:1389-1394, 2001)."

The Patent Office has now rejected (1) applicant's showing of tissue specificity, stating that it is not specific to the molecule, and (2) applicant's showing of enzyme activity, alleging that it is not a "well-known" activity. It is apparent that the Patent Office is now applying a *per se* rule, without reviewing the specific facts of the case, and without properly having solicited Notice and Comment. These actions are contrary to the Administrative Procedure Act ("APA"). Furthermore, as explained below, it is failing to follow its own published guidelines reasonably relied upon by Applicant.

Tissue-specificity was published by the Patent Office as adequate to conform to the statutory requirements to get a patent. Example 12 of the *Revised Interim Utility Guidelines Training Materials* is of a marker that is specific for a cancer – which is a type of tissue specificity. There is no reason why tissue specificity of normal tissue would not analogously satisfy the utility requirements.

Secondly, Example 6 in the *Synopsis of Application of Written Description Guidelines* described a "glial specific G-coupled protein receptor whose function is associated with glial

differentiation." See, attached Pages 278-29. Indeed, this is an example of specificity for a normal tissue. There is no indication in the example that the claim was deficient on any other §112, first paragraph, ground. If it were, it would have been entirely misleading and disingenuous of the Office not to have brought this to patent practitioners' attention.

The Utility and Written Description guidelines were issued by the Patent Office to provide direction to both the examining group and the public in how to interpret the statutory requirements to get a patent. Applicant's claimed invention has a utility which precisely meets the standards set forth in the PTO's own published guidelines. If Applicant is not to look to this material to know what is patentable, where is s/he to go?

In summary: The PTO offered examples of a tissue-specific marker (for a cancer) and of a specific cell marker. The claimed EphA6 falls into the same class of utilities, and likewise should be deemed adequate. Furthermore, Exhibits 1 and 2 establish that ephrins are widely known, recognized, and used by the scientific community. By the PTO's own standards, the claims are therefore allowable. To hold otherwise, would be in complete disregard for the published guidelines that Applicant has reasonably relied upon in filing this application.

The Patent Office can not require that such tissue specificity be disease-related. There is no law, rule, statute, or federal decision that could reasonably be interpreted as being so limited.

In view of these comments, withdrawal of the rejection is respectfully requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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